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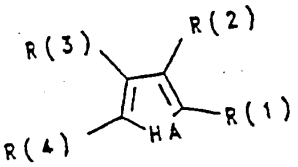
(54) **Substituierte N-Heteroaroylguanidine, als Inhibitoren des zellulären Natrium-Protonen-Antip als Antiarrhythmika und als Inhibitoren der Proliferation von Zellen.**

(57) Die Erfindung betrifft Heteroaroylguanidine der Formel I



I

worin die Substituenten HA und R(1) bis R(5) die in Anspruch 1 wiedergegebenen Bedeutungen haben. Diese Verbindungen I haben sehr gute antiarrhythmische Eigenschaften aufweisen, wie sie zum Behar Krankheiten wichtig sind, die beispielsweise bei Sauerstoffmangelerscheinungen auftreten. Die Verb sind infolge ihrer pharmakologischen Eigenschaften als antiarrhythmische Arzneimittel mit cardiop Komponente zur Infarktprophylaxe und der Infarktbehandlung sowie zur Behandlung der angina hervorragend geeignet, wobei sie auch präventiv die pathophysiologischen Vorgänge beim Entsteh misch induzierter Schäden, insbesondere bei der Auslösung ischämisch induzierter Herzarrhythmien, oder stark vermindern. Wegen ihrer schützenden Wirkungen gegen pathologische hypoxische und isch Situationen können die erfindungsgemäßen Verbindungen der Formel I infolge Inhibition des zellulare Austauschmechanismus als Arzneimittel zur Behandlung aller akuten oder chronischen durch Ischämie

EP 0 676 395 A2

LANG H
Number of Countries: 022 Number of Patents: 009
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Main IPC	Week
EP 676395	A2	19951011	EP 95105088	A	19950405	C07D-207/40	199546 B
DE 4412334	A1	19951019	DE 4412334	A	19940411	C07D-207/416	199547
AU 9516354	A	19951019	AU 9516354	A	19950407	C07D-207/416	199549
NO 9501405	A	19951012	NO 951405	A	19950410	C07D-207/416	199549
FI 9501681	A	19951012	FI 951681	A	19950407	C07D-207/34	199601
JP 7291927	A	19951107	JP 95107811	A	19950410	C07D-207/416	199602
CA 2146707	A	19951012	CA 2146707	A	19950410	C07D-207/34	199607
ZA 9502930	A	19960327	ZA 952930	A	19950410	C07D-000/00	199619
EP 676395	A3	19960306	EP 95105088	A	19950405	C07D-207/40	199624

Priority Applications (No Kind Date): DE 4412334 A 19940411
Cited Patents: No search report pub.; 3. journal ref.; DE 1965267; DE 2055727; EP 416499; EP 556672; EP 556673; EP 556674; EP 577024; EP 589336 ; EP 590455; EP 622356; EP 639573; JP 44030268; WO 9304048
Patent Details:

Patent	Kind	Lan	Pg	Filing Notes	Application	Patent
EP 676395	A2	G	48			
Designated States (Regional): AT BE CH DE DK ES FR GB GR IE IT LI LU NL PT SE						
DE 4412334	A1		41			
JP 7291927	A		28			
ZA 9502930	A		70			

Abstract (Basic): EP 676395 A
Heteroaryl-guanidine derivs. of formula (I) and their salts are new. A = S(O)m, O or NR5; m = 0, 1 or 2; R5 = H, 1-8C alkyl or CmH2mR81; R81 = 3-8C cycloalkyl, phenyl (opt. substd. by 1-3 of F, Cl, CF3, Me, OMe, and NR82R83) or 1-9C heteroaryl (bonded via C or N and opt. substd. by 1-3 of F, Cl, CF3, Me, OMe, OH, NH2, NHMe and NMe2); R82, R83 = H or Me; one of R1, R2 = CO-N=C(NH2)2; the other = H, F, Cl, Br, I, 1-3C alkyl, OR6, 1-4C perfluoroalkyl, CO-N=C(NH2)2 or NR6R7; R6,R7 = H or 1-3C alkyl; R3, R4 = (i) H, F, Cl, Br, I, CN, X(CH2)m(1-6C) perfluoroalkyl, X(CH2)mF, S(O)mR8, CONR9R10, COR11, SO2NR12R13; (ii) 1-8C alkyl, CmH2mR81; (iii) 1-9C heteroaryl (opt. substd. by 1-3 of F, Cl, CF3, Me, OMe, OH, NH2, NHMe and NMe2); (iv) -Y-C6H4-(CO)i-(CHOH)j-(CHOH)k-R23; (v) H, F, Cl, Br, I, CN, 1-8C alkyl, 1-8C perfluoroalkyl, 3-8C alkenyl, CgH2g-R26; SR29, OR30, NR31R32, CR33R34R35; (vii) -W-C6H4-R97; (viii) S(O)mR37, SO2NR38R39; (ix) X1R46; (x) SR64, OR65, NHR66, NR67R68, CHRR69R70, CR54R55-OH, Ctriple bondC-R56 C(R58) C-R57 (sic), (CR59R60)u-CO-(CR61R62)v-R63; (xi) SO2NHR76; or (xii)NR84R85; X = O, S or NR14; R14 = H or 1-3C alkyl; R8 = 1-5C alkyl, 3-6C alkenyl, CnH2nR15 or CF3; R9, R11, R12 = H or as R8; n = 0-4; R15 = 3-7C cycloalkyl or phenyl (opt. substd. by 1-3 of F, Cl, CF3, Me, OMe and NR16R17); R16,R17 = H or 1-4C alkyl; R10, R13 = H or 1-4C alkyl; or R9+R10 or R12+R13 = (CH2)4 or (CH2)5 in which one CH2 may be replaced by O, S, NH, NMe or N-benzyl; R18 = 3-8C cycloalkyl or phenyl (opt. substd. by 1-3 of F, Cl, CF3, Me, OMe and NR19R20); R19,R20 = H or Me; Y = O, S or NR22; h = 0 or 1; i, j, k = 0-4; provided that h, i and k are not all 0; R22,R23 = H or 1-3C alkyl; g = 0-4; R26 = 3-8C cycloalkyl, phenyl, biphenyl, or naphthyl (where aromatics are opt. substd. by 1-3 of F, Cl, CF3, Me, OMe and NR27R28); R27,R28 = H, 1-4C alkyl or 1-4C perfluoroalkyl; R29-R31, R33 = -(CH2)m- (1-9C) heteroaryl (opt. substd. as in R81); R32, R34 , R35 = H, 1-4C alkyl, 1-4C perfluoroalkyl, or as R29; R96 = heteroaryl as defined for R81, or benzyl; W = O, S or NR36; R36 = H or 1-4C alkyl; R37 = 1-8C alkyl, 1-8C perfluoroalkyl, 3-8C alkenyl or -CsH2s-R40; s = 0-4; R40 = as R26; R38 = H, 1-8C alkyl, 1-8C perfluoroalkyl, 3-8C alkenyl or -CwH2w-R26; R39 = H, 1-4C alkyl or 1-4C perfluoroalkyl; or R38+R39 = (CH2)4 or (CH2)5, in which one CH2 may be replaced by O, S, NH, NMe or N-benzyl; X1 = O, S, NR47, (D=O)A'- or NR48C=MN*(R49)-; M = O or S; A' = O or NR50; D = C or SO; R46, R49 = 1-8C alkyl, 3-8C alkenyl, -(CH2)b-(1-7C)perfluoroalkyl or -CxH2x-R26; b = 0 or 1; x = 0-4; R47, R48, R50 = H, 1-4C alkyl or 1-4C perfluoroalkyl; or R46+R47 or R46+R48 = (CH2)4 or (CH2)5 in which CH2 may be replaced by O, S, NH, NMe or N-benzyl; A' and N* are bonded to the phenyl ring of the benzoylguanidine structure; R64-R67, R69 = -(CH2)y-(CHOH)z-(CH2)q'-(CH2OH)t-R71 or -(CH2)b'-O-(CH2CH2O)c'-R72; R71,

R72 = H or Me; b', c' are not defined; u, t = 1-4; v, y, z, a' = 0-4; R68, R70, R54, R55 = H or 1-6C alkyl; or CR69R70 or CR54R55 = 3-8C cycloalkylidene; R63 = H, 1-6C alkyl, 3-8C cycloalkyl or -CeH2e-R73; e = 0-4; R80 = 5-7C cycloalkyl or phenyl (opt. substd. by 1-3 of F, Cl, CF3, OMe and 1-4C alkyl); or R77+R78 = (CH2)4 or (CH2)5, in which one CH2 may be replaced by O, S, NH, NMe or N-benzyl; R79 = as R77; or amidino; R84, R85 = H or 1-4C alkyl; or R84+R85 = (CH2)4 or (CH2)5 in which one CH2 may be replaced by O, S, NH, NMe or N-benzyl or 1 or 2 CH2 gps. may be replaced by CH-Cd'H2d'+1; d' is not defined. Cpds. (I; A = O; R1 = -CON=C(NH2)2; R2, R3 = H; R4 = H, Me or Et) are excluded.

USE - (I) are used for treatment of arrhythmia or shock states; for treatment or prophylaxis of cardiac infarct, angina pectoris, cardiac ischaemia, ischaemic states of the peripheral and central nervous system, stroke or ischaemic states of the peripheral organs and limbs; and adjuvant during surgical operations and organ transplants; in preservation and storage of transplants; for treatment of diseases in which cell proliferation is a prim. or sec. cause, esp. atherosclerosis, complications following diabetes, cancer, fibrotic diseases, (e.g. fibrosis of the lungs, liver or kidneys) or prostatic hyperplasia; and as reagents for inhibiting Na+/H+ exchange and for diagnosis of hypertension and proliferative diseases (all claimed). More generally (I) inhibit the cellular Na+/H+ exchange mechanism and cell proliferation and are useful for combatting oxygen deficiency states, pathological hypoxia and ischaemia. They are esp. useful as antiarrhythmic agents.

Daily dose is 0.001-10 (pref. 0.01-1) mg orally, parenterally, rectally or by inhalation.

ADVANTAGE - (I) have good antiarrhythmic activity, without undesirable salidiuretic side effects, potent cellular Na+/H+ exchange inhibiting activity and good water solubility (facilitating i.v. admin.).

Dwg.0/0

Abstract (Equivalent): DE 4412334 A

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Dwg.0/0

Derwent Class: B03

International Patent Class (Main): C07D-000/00; C07D-207/34; C07D-207/40; C07D-207/416

International Patent Class (Additional): A01N-001/02; A61K-031/33; A61K-031/34; A61K-031/38; A61K-031/40; A61K-031/415; A61K-031/44; A61K-031/445; A61K-031/47; A61K-049/00; C07D-307/68; C07D-333/38; C07D-333/48; C07D-401/00; C07D-401/04; C07D-401/12; C07D-403/02; C07D-403/04; C07D-403/12; C07D-405/02; C07D-405/04; C07D-405/12; C07D-409/02; C07D-409/04; C07D-409/12; C07D-521/00

5/7/2

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New and known thienyl urea or isourea derivs. - used as animal growth promoters

Patent Assignee: BAYER AG (FARB)

Inventor: BERSCHAUER F; DEJONG A; HALLENBACH W; LINDEL H; SCHEER M

Number of Countries: 019 Number of Patents: 013

Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Main IPC	Week
DE 3529247	A	19861120	DE 3529247	A	19850816		198648 B
EP 202538	A	19861126	EP 86106209	A	19860506		198648
AU 8657217	A	19861120					198702
JP 61268678	A	19861128	JP 86109713	A	19860515		198702
DK 8602300	A	19861118					198707
BR 8602224	A	19870113					198708
ZA 8603645	A	19861110	ZA 863645	A	19860520		198708
FI 8602201	A	19861118					198711
HU 41244	T	19870428					198721